IN THE DRAWINGS

The attached sheet of drawings (Sheet 4 of 9) includes changes to Table 3. This sheet, which includes Table 3, replaces the original sheet including Table 3. Corrections to the column heading labels have been made.

Attachment: Replacement Sheet

REMARKS

Entry of the foregoing amendment and favorable reconsideration of the subject application, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested. This amendment is in response to the non-final Office action mailed on August 3, 2009. Claims 1 and 8 have been amended, claim 6 has been canceled, and claims 4 and 5 are pending.

Foremost, Applicants have amended Table 3 (Sheet 4 of 9) to correct typos in the column headings. Table 3 provides a listing of the formulation components of Comparative Examples 1 and 2. The column headings, however, reciting "Formulation 16" and "Formulation 17" have been amended to correctly recite "Comparative Example 1" and "Comparative Example 2", respectively. No new matter has been added. Entry of the Replacement Sheet is respectfully requested.

Rejections Under 35 U.S.C. § 112

The Examiner has rejected claim 8 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. *Office Action*, pp. 2-3. Specifically, the Examiner believes there is no support for the claim recitation "wherein said first and second skin layers are selected to provide a pH-independent release of said beraprost sodium." *Id.* at 3. The Examiner also alleges that there is no support for the limitation "beraprost sodium composition with high bioavailability and pH sensitivity." *Id.* Applicants respectfully disagree.

The claimed invention is directed to a sustained release formulation having stable drug-releasing and absorbing properties "where fluctuation [of beraprost sodium release] depending on the location in the entire digestive tract is small." *Application* at ¶[0011]. The specification describes

the release of beraprost sodium (BPS) from the formulation as "independent of the pH of the digestive tract." *Id.* Moreover, the disclosure provides specific examples where "skin layer" components are selected to provide pH-independent release of BPS. Applicants even compare the properties (*e.g.* release rate and bioavailability) of the claimed formulations to those known in the art. *See* ¶¶[0080], [0085] and [0086]. For Example, ¶[0086] demonstrates that the sustained release formulations according to the claimed invention "attain stable continuous release irrespective of pH." Accordingly, since Applicants have shown possession of the claimed invention, *i.e.* pH-independent release of beraprost sodium, this rejection should be withdrawn.

The Examiner has also rejected claims 1 and 4-8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner contends that the term "softening point" does not appear to be a term of art. *Office Action*, pp. 2-3. Applicants respectfully disagree and submit that the term "softening point" is an established technical term describing a particular physical property of a substance, and is widely used in the fields of oils and waxes. Indeed, measurement of the "softening point" is well known in the art, as shown in the enclosed reference. *ASTM D6090 reference*. The American Society for Testing Materials (ASTM) and the German Institute for Standardization (DIN) even indicate that the "softening point" can be determined by using a Mettler "cup and ball apparatus." *Id.* Accordingly, one skilled in the art would understand what is meant by the term "softening point" and, thus the rejection over claims 1 and 4-8 should be withdrawn.

The Examiner also alleges that the term "high bioavailability" in claim 8 is indefinite. To expedite prosecution, claim 8 has been amended to remove this term from

the preamble. Therefore, the rejection over claim 8 should also be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1 and 4-8 under 35 U.S.C. § 103(a) as being unpatentable over *Hara* (JP 02225416) in view of *Samejima* (U.S. Patent No. 5,068,112) and *Gowan* (U.S. Patent No. 5,406,617). The Examiner has also rejected the claims over *Hara* in view of *Liversidge* (U.S. Patent No. 5,145,684) and *Kokubo* (JP01287021). The Examiner has similarly rejected the claims over Hara in view of *Liversidge* and *Araume* (JP59020219). Applicants respectfully traverse each of these rejections and submit that even if the teachings of the collective references were combined in the manner suggested by the Examiner, the combinations would still not result in the claimed invention.

Hara* in view of *Samejima* and *Gowan

Hara does not disclose the pH-independent release of BPS or the use of the water-insoluble acrylic polymer derivatives of the claimed invention. *Hara* is directed to an oral formulation comprising granules of a PGI_2-derivative which are coated with an enteric and/or water-insoluble material to provide sustained release granules. *Hara*, page 4. As examples of enteric coating materials, *Hara* recites various polymers including methacrylic acid-methyl methacrylate copolymer (having a solution pH in the range of 6-7), methacrylic acid-ethyl acrylate copolymer (having a solution pH of 5.5), and methylceullulose derivatives (having a solution pH in the range of 5-5.5). *Id.* at 7. Each of these materials are pH-dependent polymers which, given the recited pH ranges, are hardly soluble in acidic conditions (but soluble in neutral conditions). Thus, the use of these enteric materials, alone or in combination with

other disclosed water-insoluble materials, provides for a pH-dependent release. Accordingly, *Hara* does not disclose the sustained release of BPS in a pH-independent manner as in the claimed invention or the use of the claimed water-insoluble acrylic polymer derivatives in a first "skin layer."

In fact, there is no disclosure in *Hara* of combining any material with a PGI_2-derivative to ensure sustained release, let alone a pH-independent release. PGI_2-derivatives, including BPS, are acidic active pharmaceutical ingredients (APIs) which have pH-dependent solubilities. Applicants have shown in Comparative Example 2 that when water-insoluble materials, such as those disclosed in *Hara*, are combined with an API having a pH-dependent solubility, the formulation exhibits a pH-dependent release of API. Because of this, prior art formulations failed to provide stable, sustained release of BPS with satisfactory bioavailability. *Application*, ¶¶[0085]-[0090]. As demonstrated in Formulation Examples 16, 17, and 18 and Test Examples 1 and 2, the claimed invention overcomes the deficiencies of the prior art and allows for sustained release of BPS in a manner which is not influenced by pH, while providing higher bioavailability than prior art formulations. *Id.* at ¶¶[0080]-[0090]. There is no disclosure in *Hara* to incorporate any of the claimed "skin layer" components or any material which would cause the PGI_2-derivative to be released in a pH-independent manner. In fact, Hara provides no mention of pH-independent release at all and certainly no disclosure that such a property is even desirable. Consequently, one skilled in the art would not look to *Hara* for any guidance to make the sustained-release BPS formulation of the claimed invention.

Neither *Samejima* or *Gowan* cure the deficiencies of *Hara*. *Samejima* is directed to a controlled release pharmaceutical preparation comprising a core containing an API and a porous film coating comprising either (1) a hydrophobic

polymeric substance, or (2) a combination of a hydrophobic polymeric substance and a hydrophilic polymeric substance. *Samejima*, abstract. *Samejima* discloses many examples of different hydrophobic and hydrophillic polymers which could be utilized to provide films having varying porosities and hence, different API release rates. *Id.* at col.2 to col.13; col.6 ll.37-45. In this regard, *Samejima* discloses the application of polymer films to control API release much like in Comparative Example 2 of the claimed invention. And, as already detailed above, such porous film coatings cannot offer a sustained release of an API having a pH-dependent solubility. Moreover, *Samejima* provides no disclosure to pick and choose any specific combination of polymers to ensure a pH-independent release, let alone to select any of the "skin layer" components of the claimed invention. Therefore, even if the teachings of *Samejima* were combined with *Hara*, the combination would not result in the claimed invention.

Gowan is directed to a technique for taste masking granules by coating them with a hot-melt base material. *Gowan*, col.1 ll.7-12. *Gowan* does not disclose that any of the hot-melt base materials can be selected to alter the drug release profile of a formulation, let alone to provide a sustained release of BPS as in the claimed invention. Nor is there any disclosure that adding a taste-masking hot-melt base material could allow for pH-independent release of an API having a pH-dependent solubility. Accordingly, even if the collective teachings of *Hara*, *Samejima*, and *Gowan* were combined, the combination would not result in the claimed invention. Moreover, even after *KSR v. Teleflex*, 550 U.S. 398, 402 (2007), it is not enough that certain elements could be combined. There must be some reason to suppose that they would be combined and nothing in the collective teachings of the cited art leads to the conclusion that the films of *Samejima* or materials of *Gowen* would be

combined with the formulation of *Hara* to provide for a sustained release of BPS as in the claimed invention. Therefore, the rejection should be withdrawn. *See* also *U.S. v. Adams*, 383 U.S. 39, 50-52 (1965).

Hara* in view of *Liversidge* and *Kokubo

Applicants submit that that even if *Hara*, *Liversidge*, and *Kokubo* were combined, the collective teachings would not result in the claimed invention. As already recited above, *Hara* does not teach the use of the claimed water-insoluble acrylic polymer derivatives or the sustained release of BPS in a pH-independent manner. Neither *Liversidge* nor *Kokubo* cure this deficiency.

Liversidge is directed to stable, dispersible drug nanoparticles and a method for preparing such particles by wet milling. *Liversidge*, col.3 ll.16-31. The reference as a whole does not disclose the modification of a formulation to provide a sustained release of an API. Indeed, there is no disclosure in *Liversidge* that modifying particle size would result in the sustained release of BPS as in the claimed invention. Nor is there any disclosure in *Liversidge* of combining any water-insoluble acrylic polymer derivatives with BPS to provide sustained release as in the claimed invention.

Kukobo is directed to a masking technique where a hot-melt base material is coated on granules. *Kukobo*, Abstract. *Kukobo* does not disclose that any of these hot-melt base materials can be selected to alter the drug release profile of a formulation, let alone to provide a sustained release of an API. Nor is there any disclosure that adding a hot-melt base material would allow for pH-independent release of an API having a pH-dependent solubility. Accordingly, even if the collective teachings of *Hara*, *Liversidge*, and *Kukobo* were combined, the

combination would not result in the claimed invention and, thus the rejection should be withdrawn.

Hara* in view of *Liversidge* and *Araume

Applicants submit that that even if *Hara*, *Liversidge*, and *Araume* were combined, the collective teachings would not result in the claimed invention. As already recited above, *Hara* does not teach the use of the claimed water-insoluble acrylic polymer derivatives or the sustained release of BPS in a pH-independent manner. *Liversidge* does not provide any disclosure that modification of particle size would result in a sustained release of BPS as in the claimed invention. Neither does *Araume* cure the deficiency of *Hara*.

Araume discloses a technique to prevent deterioration of the performance of an enterosoluble coating of a solid pharmaceutical during storage by undercoating the dosage form with a higher fatty acid, followed by coating with an enterosoluble coating. *Araume*, Abstract. First, *Araume* explicitly teaches the use of a enterosoluble coating which, as described above, is pH-dependent. Further, *Araume* is directed to maintaining the pH-dependent release of enterosoluble granules exhibiting pH-dependent behavior. *Araume* offers nothing to one looking to provide a sustained release of BPS, let alone a pH-independent release. *Id.* Thus, the disclosure of *Araume* is diametrically opposed to the claimed invention and one skilled in the art would not look to *Araume* to create the sustained release BPS formulation of the claimed invention. Therefore, because the Examiner has not established a *prima facia* case of obviousness, the rejection should be withdrawn.

In conclusion, Applicants submit that the collective teachings of the cited art do not disclose the use of the water-insoluble acrylic polymer derivatives to provide sustained release of BPS as in the claimed invention. Moreover,

Applicants further submit that the collective teachings of the cited art do not disclose the pH-independent, sustained release of BPS as in the claimed invention.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: February 3, 2010

Respectfully submitted,

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Table 3 Comparative Examples 1 and 2

Constitution	Function	Components	Comparative Example 1	Comparative Example 2
Nucleus	Nucleus Granule	NONPAREIL	97.27	89.86
Drug-Carrying Layer	Drug	Beraprost Sodium	0.12	0.12
	Coating Agent	HPMC 2910	2.37	2.37
	Plasticizer	PEG 6000	0.24	0.24
	Subtotal		100.00	2.73
Sustained Release Skin Layer	Coating Agent	Eudragit RS-100		3.97
		Eudragit RS-100L		1.32
	Plasticizer	triethyl citrate		0.53
	Brittleness Agent	Talc		1.59
	Subtotal			7.41
Other	Lubricant	Talc	0.50	0.50
Total			100.50	100.50

Unit: mg/capsule